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## Examining the relationship between Hormone therapy(HT) and dry-eye syndrome in post-menopausal women- A cross-sectional comparison study

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Objective:</b> To examine the relationship between hormone therapy (HT) and dry-eye syndrome (DES) in post-menopausal women.</p> <p><b>Methods:</b> A cross-sectional study was performed on 360 postmenopausal women. They were grouped into two groups. Group 1 was the control (n=189) without DES symptoms and did not receive HT treatment. Group 2 (n=177) women with DES symptoms. Group.2 was randomly grouped into two categories. Group 2A (n=90) that received estrogen-only HT, and Group 2B (n= 87) who treated with a combination of estrogen and progesterone HT. The severity of symptom levels was determined using the OSDI index levels that identify the extent of the relationship between sex hormones and DES. A further comparison of the severity symptoms among women under HT and those not under HT was used to establish the relationship between HT and DES in post-menopausal women.</p> <p><b>Results:</b> i) a significant variation in the severity levels of DES across women not under HT and those who under HT (G2A) and HT (G2B) [F(2, 357)= 974.186, p=.000], ii) a significant variation in the severity levels of DES based on dosage levels (&lt;1 mg/day and &gt;1 mg/day) across women under HT (G2A) and HT (G2B) [F(2, 357)= 302.513, p=.000]; and iii) a significant variation in the severity levels of DES based on duration levels 12, 36 and 48 months) across women under HT (G2A) and HT (G2B) [F(3, 356)= 218.266, p=.000].</p> <p><b>Conclusion:</b> The current study findings have negated the previous assumption that HT use contributes to a reduction in DED symptoms among postmenopausal women. Instead, prolonged HT use appears to increase the risk of DED.</p>

**Cover letter**

**Dear Mrs. Susan Keefe (assistant Editor)**

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We wish to thank you for your interest in our manuscript entitled “**Examining the relationship between hormone (HT) and dry-eye syndrome in post-menopausal women- A cross-sectional comparison study**”

**We have done the change according to your suggestion On the figure and Tables the word Oestrogen has been changed to Estrogen.**

**Hormone replacement therapy (HRT) has been changed to Hormone therapy (HT).**

**Besides a short summary about the article for the journal table of content has been written.**

Thank you very much in advance for your help and guidance

Prof. Dr. ME. Hammadeh

## **Response to the Reviewers**

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### **Paper Summary**

Hormone therapy has gained popularity as a ministration method for menopause-related complaints. However, its potential to increase the risk of dry-eye syndrome (DES) requires further investigation. Findings from the current cross-sectional research suggest that HT is not a protective factor against the severity of DES in postmenopausal women. As such, the findings from the current study should be used to educate healthcare providers and postmenopausal women with DES regarding the credibility of HT. Further research is needed to develop solutions regarding the risks of HT or to develop more effective treatments related to menopause.

Thank you very much in advance for your help and guidance

Prof. Dr. ME. Hammadeh

# **Examining the relationship between hormone therapy (HT) and dry-eye syndrome in postmenopausal women: A cross-sectional comparison study**

Running Title: Hormone therapy and dry-eye syndrome

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**Objective:** To examine the relationship between hormone therapy (HT) and dry-eye syndrome (DES) in post-menopausal women.

**Methods:** A cross-sectional study was performed on 360 postmenopausal women. They were grouped into two groups. Group 1 was the control (n=189) without DES symptoms and did not receive HT treatment. Group 2 (n=177) women with DES symptoms. Group 2 was randomly grouped into two categories. Group 2A (n=90) that received estrogen-only HT, and Group 2B (n= 87) who treated with a combination of estrogen and progesterone HT. The severity of symptom levels was determined using the OSDI index levels that identify the extent of the relationship between sex hormones and DES. A further comparison of the severity symptoms among women under HT and those not under HT was used to establish the relationship between HT and DES in post-menopausal women.

**Results:** i) a significant variation in the severity levels of DES across women not under HT and those who under HT (G2A) and HT (G2B) [ $F(2, 357)= 974.186, p=.000$ ], ii) a significant variation in the severity levels of DES based on dosage levels (<1 mg/day and >1 mg/day) across women under HT (G2A) and HT (G2B) [ $F(2, 357)= 302.513, p=.000$ ]; and iii) a significant variation in the severity levels of DES based on duration levels 12, 36 and 48 months) across women under HT (G2A) and HT (G2B) [ $F(3, 356)= 218.266, p=.000$ ].

**Conclusion:** The current study findings have negated the previous assumption that HT use contributes to a reduction in DED symptoms among postmenopausal women. Instead, prolonged HT use appear to increase the risk of DED.

**Key Words:** Dry-eye syndrome; Hormone therapy; postmenopausal women

## Introduction

Menopause is a natural decline in reproductive hormones when a woman reaches her 40s or 50s.<sup>1</sup> This phase marks the end of a woman's reproductive years because a woman's body slowly produces less of the hormones estrogen and progesterone<sup>2</sup>. According to Moulton et al.

<sup>57</sup> More than 30 million women in the United States are now in or past menopause, and another 6 million women will enter menopause during the next decade. Menopause and its corresponding transitional phases impact the physical and psychological subsistence of women, and studies on the symptoms and effects of menopause identify adverse effects on women's physical performance<sup>3</sup> and occupational performance<sup>4</sup> reduced health<sup>5</sup> with diseases such as cardiovascular<sup>6,7</sup>, and osteoporosis<sup>8,9</sup>, along with depression<sup>10,11,12</sup> and loss of quality of life.<sup>13,14,15,16</sup> Dry-eye syndrome (DES) is another risk factor associated with menopause<sup>17,18</sup> and DES or Kerato Conjunctivitis Sicca (KCS) can be defined as group of conditions of the ocular surface and tears which produce aberrations in the tear film, resulting in perpetual visual discomfort and disturbances with eventual potential to damage the ocular surface.<sup>19</sup>

Characterized by clinical symptoms such as consistent "ocular burning, foreign body sensation, stinging sensation, pain, photophobia or blurred vision"<sup>20</sup> the resulting outcome exposes the individual to red eyes, pain and eventual fatigue.<sup>21</sup> Given the broad range of symptoms, the attribution of DES as a "multifactorial ocular disease"<sup>19</sup> can be validated in this regard and the detrimental impacts of DES on the quality of health<sup>22,23,24,25</sup> and vision<sup>26</sup> of the affected individuals compounded by various epidemiological studies can be indicatively established to outline a crucial claim that, DES has the potential to impair normal functioning of individuals.

Apart from environmental, physiological and pathological causes, hormonal changes can also be attributed to DES<sup>20</sup>. A number of studies have identified a relationship between sex hormones and DES<sup>27-32</sup> especially in postmenopausal women. In a study conducted by Jones-Jordan and Nichols, it was revealed that nearly 63% of the evaluated 939 postmenopausal women suffered from eye dryness. Such findings further emphasize the need for identifying the extent of the relationship between sex hormones and dry eye, given: i) the common presence of DES in the population<sup>34</sup> and ii) considering that post-menopausal women experience severe hormonal changes, given the aberrations in the endocrine systems of women<sup>35</sup> and subject themselves to various treatments to maintain a certain balance in their daily lives. One such treatment that has gained wide popularity is Hormone therapy (HT).

HT refers to a regular administration of hormones-estrogen and progesterone to post-menopausal women to minimize the physical and psychological effects of menopause<sup>36</sup>. HT has gained popularity as a ministrations method for menopause related complaints<sup>36</sup> and previous studies popularized cardiovascular improvement and bone density and lipid metabolism improvement as other beneficial effects of HT<sup>36</sup>. However, critics have expressed their concern about the detrimental effects of HT.<sup>37-39</sup> For example, potential relationships between HT and cancer risk and HT and DES have been established<sup>40,41</sup>. Literature on the relationship between HT and DES reflect both the advantages and risks of HT on dry eye. Certain studies indicate the risks of HT and claim that HT with estrogen and estrogen with progesterone has increased risks of DES in women<sup>41</sup>. However, certain other studies<sup>42,43</sup> reflect otherwise. Despite the various study findings, the relationship between DES and HT is still a debatable subject because a gap still exists in this field. The current study aims to bridge the gap and adds to the existing literature by examining the relationship between hormone therapy (HT) and dry-eye syndrome in postmenopausal women through a comprehensive a cross-sectional comparison study.

**Hypothesis:** There is a correlation between HT use and a reduction in DES severity in postmenopausal women.

## Materials and Methods:

A cross-sectional study was performed on 360 postmenopausal women (aged 49 years and above) for a period of 2 years based on a database of 2,000 postmenopausal women who had visited the clinics in the past 4 years.

Data of the participants was collected from 30 Gynaecological clinics with the majority of the information obtained from Tawam Hospital in affiliation with John Hopkins International Clinic (Al Ain) (n=93), Germany Homburg Saar (n=62), SKMC Sheikh Khalifa Hospital managed by Cleveland Clinic (Abu Dhabi) (n= 53), Al Ain Hospital (Al Ain City) (n=37) The rest of the data from (n=115) participants came from the remaining 26 clinics. Each clinic was asked to provide 14 post- menopausal women (7 not under HT and 4 under estrogen alone and 4 under estrogen and progesterone) suffering from DES, with an estimate of 360 sample size.

The participants were grouped into two groups. Group 1 was the control composed of (n=189) subjects without DES symptoms and did not receive HT treatment. Group 2 included (n=177) women with DES symptoms that were randomly grouped into two categories. Group 2A included 90 subjects that received estrogen-only HT, and Group 2B consisted of 87 subjects treated with a combination of estrogen and progesterone HT. The severity of symptom levels was determined using the OSDI index levels of normal, mild, moderate and severe that identifies the extent of the relationship between sex hormones and DES. A further comparison of the severity symptoms among women under HT and those not under HT was used to establish the relationship between HT and DES in post-menopausal women.

To ascertain the presence of DES in women, two questions pertinent to frequency of eyes getting dried or irritated and clinical diagnosis of DES, based on studies concerning hormone therapy and dry-eye conducted by Schaumberg et al.,<sup>41</sup>. Only women that complained of 'constant' feeling of dryness and feeling of dryness often or sometimes were asked to take a survey based on IDEEL dry-eye symptoms bother module. Subjects with DES-inducing conditions such as diabetes, hypertension, depression, rheumatoid arthritis, users of systematic or topical medications, and contact lens wear were excluded from the study.

Choosing survey method as the primary data collection method for data collection was based on the understanding that assessing the presence of relationship between symptoms and signs of DES remains as an issue<sup>19,27,33,44-48</sup> which questions the reliability of the tests. Even if the clinical tests achieve to establish a relationship, assessing the severity of the DES is very poor<sup>44,50-54</sup>. Thus, a study that practically applied the IDEEL survey developed by Abetz et al<sup>55</sup>. The development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients to present a cohort assessment of the symptoms of DES was considered as an apt contextual requirement. No doubt, the symptoms presented in the Ocular Surface Disease Index (OSDI)<sup>56</sup> assess the presence of DES; however, the detailed list of symptoms in the IDEEL survey ensures the comprehensiveness and validity of the current study.

A combination of IDEEL survey for collecting data (demographical and DES symptoms) from the postmenopausal women and use of OSDI index to measure the severity levels of DES in postmenopausal women under HT and not under HT proved as a unique contribution to the literature. A novel aspect in the field, each of the 360 participants' OSDI score was calculated on a scale of 0-100. The OSDI score was calculated based on the OSDI formula: 
$$\text{OSDI score} = (\text{sum of scores}) * 25 / (\text{number of questions answered}).$$

With a range of severity levels based on percentile deviation, the OSDI scores of the postmenopausal women and their respective groups were assorted under mild ( $<25$ ), moderate (in and around 50) and severe levels ( $>75$ ). The obtained results were further subjected to statistical analysis using SPSS software, where descriptive statistics, ANOVA and post hoc analysis using Welch and Brown-Forsythe tests were conducted



## Results

An overview of the collected demographic data establishes a direct relationship between HT usage, and demographic and social characteristics (Tab. 1). HT usage is prevalent among younger women with greater educational qualification and income. As hypothesized, the frequency of eye examinations of post-menopausal women under HT was higher than women not under HT in the past 2 years irrespective of the duration and dosage of HT. Only 8.9% of the respondents belonged to normal range of the OSDI index (below 11.5 score based on OSDI index)<sup>56</sup>, establishing the presence of mild, moderate or severe symptoms of DES among the remaining participants.

Post hoc comparisons indicated that mean score for postmenopausal women not under HT ( $M = 22.76$ ,  $SD = 11.92765$ ) was significantly different than postmenopausal women under HT estrogen only ( $M = 92.52$ ,  $SD = 12.93711$ ) and postmenopausal women under HT estrogen and progesterone ( $M = 50.89$ ,  $SD = 12.44588$ ). On similar lines, post hoc comparisons also indicated that mean score for postmenopausal women with  $<1\text{mg/day}$  HT dosage ( $M = 69.032$ ,  $SD = 25.48232$ ) was significantly different than postmenopausal women  $>1\text{mg/day}$  HT dosage ( $M = 74.082$ ,  $SD = 23.56768$ ). Post hoc comparisons also indicated that mean score for postmenopausal women with 12 months HT treatment ( $M = 61.23$ ,  $SD = 25.93619$ ) was significantly different than postmenopausal women with 36 months HT treatment ( $M = 77.641$ ,  $SD = 24.24393$ ) and 48 months HT treatment ( $M = 75.116$ ,  $SD = 21.95054$ ).

Welch and Brown-Forsythe tests were conducted to indicate the significance levels of any non-normal distributed data. The combined results of the three ANOVA tests and their respective descriptive statistics is indicated in the below table. Analysis of variance (ANOVA) showed: i) significant variation in the severity levels of DES across women not under HT, under HT (estrogen alone) and HT (estrogen and progesterone) [ $F(2, 357) = 974.186$ ,  $p = .000$ ] (Tab. 2; Fig. 1). Users of HT include only current users with the most recent assigned therapy. Variation in the severity levels of DES across the three categories of HT were significant in accordance with the severity definition of mild, moderate and severe ( $p < 0.001$ ).

Besides, a significant variation in the severity levels of DES based on dosage levels ( $<1\text{ mg/day}$  and  $>1\text{ mg/day}$ ) across women under HT (estrogen alone) and HT (estrogen and progesterone) [ $F(2, 357) = 302.513$ ,  $p = .000$ ] (Tab. 3 Fig. 2). Dosage levels include only current users with the most recent dosage levels. Variation in the severity levels of DES across the two categories of HT were significant in accordance with the dosage definition of  $<1\text{ mg/day}$  and  $>1\text{ mg/day}$  ( $p < 0.001$ ).

Moreover, a significant variation in the severity levels of DES based on duration levels 12, 36 and 48 months) across women under HT (estrogen alone) and HT (estrogen and progesterone) [ $F(3, 356) = 218.266$ ,  $p = .000$ ] (Tab 4; Fig. 3). Duration of HT includes only current users under HT for  $\leq 48$  months. Variation in the severity levels of DES across the two categories of HT were significant in accordance with the duration definition of 12, 36 and 48 months ( $p = 0.000$ ).

## DISCUSSION

Postmenopausal women undergo severe physical, psychological and physiological changes that require certain treatments to accomplish daily functionalities. While hormone therapy (HT) has gained popularity as a ministration method for menopause related complaints, its potential to increase the risk of dry-eye syndrome (DES) requires further investigation. DES has the potential to impair normal functioning of individuals, and study validating the relationship between sex hormones and dry eye, especially in postmenopausal women and HT and DES in postmenopausal women is essential to add to the literature in obstetrics and gynaecology fields regarding the relationship between DES and HT.

This present cross-sectional comparison study practically applied the IDEEL survey and OSDI analytical method to examine the relationship between hormone therapy (HT) and dry-eye syndrome in post-menopausal women. Unique contribution to literature is the presence of obvious increased eye examinations of post-menopausal women under HT in the past 2 years irrespective of the duration and dosage of HT. The results of the present study showed the presence of a significant relationship between sex hormones and DES with mild, moderate or severe symptom in postmenopausal women (Tab 3; Fig. 2). Also these results are in accordance with various studies<sup>20, 27-34</sup> that have scientifically validated the relationship between sex hormones and DES.

Besides, the statistical analysis showed significant variation in severity levels of DES clearly indicated that women under HT estrogen only were at higher risk than women under HT estrogen and progesterone. The presence of mild levels of DES among women not under HT clearly indicates that women under HT need to reassesses their acceptance of menopausal treatments to avoid ocular surface discomforts. This is in line with studies that indicate possible relationship between HT and increased risks of DED, especially for women under estrogen only treatment<sup>41</sup> and refutes the studies that fail to establish relationship between HT and DED.<sup>42,43</sup> One of the possible explanation for lack of this correlation in the current study is that Schaumberg et al<sup>41</sup> base their conclusions on the patient's symptoms and the self-reported clinical diagnosis. In the current study, all the patients were subjected to ocular exam for dry eye syndrome by the same clinician. Such an approach reduced the selection bias and standardized the dry eye diagnosis criteria. According to Schaumberg et al<sup>41</sup> another possible variation can be explained by the lack of relationship between HT and reduced dry eye symptoms may be attributed to genetic makeup of the study subjects.

### Study Limitation

The study has a number of potential limitations. First, the study did not control for the various DES symptoms despite the fact that the signs are not necessarily unique to DES. Other conditions also feature DES-like symptoms, such as conjunctivochalasis, recurrent corneal erosions, various neuropathies, epithelial basement membrane dystrophy, and Parkinson's disease. Second, the paper is further limited by the fact that the OSDI was the key component of the study. One limitation of the OSDI is that it only includes some dry eye symptoms such as grittiness, sensitivity to light, and pain but does not include other symptoms such as foreign body sensation and tearing.<sup>58,59 14</sup> It also only discusses some of the effects of DED on vision-related functioning; therefore, it may not capture the entire effect of DED on a patient's daily living.<sup>58</sup> In addition, OSDI responses are limited to measures of frequency (rather than to frequency and severity).<sup>60</sup> A second limitation of the OSDI that can affect the interpretation of the results is that the effort required to complete and score the scale, which may consume valuable clinic time in a practice.<sup>61</sup>

Another limitation is that there was no control made for the different dry eye diseases or types, environmental stress, climate, diurnal variations, and the individual lifestyle changes and patterns. Moreover, scholars<sup>58,60</sup> continue to point out that the DED severity measurements

widely differ, stressing the importance of averaging the results three times to obtain a more reliable figure. The current study also performed a single eye osmolality test on each eye at the time of the visit. As such, future studies undertaking three successful measurements on each eye may yield more reliable study findings. Lastly, the study did not include the epidemiological aspect across different ethnic or racial backgrounds to assess its possible effect on the DED severity among women receiving HT during the treatment duration.

**Conclusion:** The research findings have failed to establish the previous assumption that HT use contributes to a reduction in DED symptoms among postmenopausal women. Rather, the use of HT among postmenopausal women for a prolonged period of time appear to increase the risk of DED.

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**Legend for the figure**

**Figure 1.** Illustrate the severity levels of DES among the study participants and their relationship to HT treatment.

Subjects that were administered with estrogen-only HT appear to have a higher OSDI compared to the subjects using a HT combination of estrogen and progesterone HT.

**Figure 2:** Presents the severity levels which appear to be higher in subjects using more than 1 mg/day of estrogen only HT, than subjects taking the same dosage of estrogen and progesterone HT. In addition, the severity is higher in subjects taking less than 1 mg/day estrogen only HT than in those taking the same dosage of estrogen and progesterone.

**Figure 3:** shows that women who received estrogen only HT in this duration appears to show high severity levels than the other study subjects. Prolonged use of the HT appears to increase the severity levels of the DES in postmenopausal women.





**Table 1: Demographic data showing HT users and non-users in the study**

	Dry eye	Non-Dry eye	Total	<i>p</i> value
Age (years)				
Mean (SD)			55.89±11.89	
Education, n (%)				0.870
Primary	10 (2.8)	15(4.2)	25 (7.0)	
Intermediate	9 (2.5)	13(3.6)	22 (6.1)	
Secondary	14 (3.9)	18(5.0)	32 (8.9)	
Graduate	114 (31.7)	109 (30.2)	223 (61.9)	
Post Grad	30 (8.3)	28(7.8)	58 (16.1)	
HT, <i>n</i> (%)				0.003
Group 1 HT (-)	0	183 (50.8)	183(50.8)	
Group 2A HT (+) Estrogen-only	90(25.0)	0	90(25.0)	
Group 2B HT (+) Estrogen/progesterone	87(24.2)	0	87(24.2)	

A total of 177 subjects received HT treatment, while the control group of 183 subjects did not receive any HT. The participants aged 49 years and above with a mean age being 55.89±11.89 years old. The graduates (61.9%) formed more than half of the study population followed by post-graduates (16.1%), secondary (8.9%), Primary (7%) and intermediate (6.1%) school leavers, Table 1.

**Table 2: A comparison of the severity of DED between HT users after a 48 month treatment period. There was a statistically significant difference between Group 2A and Group 2B. Estrogen and progesterone HT users (Group 2B) showed significant reduction in the number of patients with DED symptoms than estrogen-only users (Group 2A) (p=0.001).**

	N	Tear Osmolality (mOsm/L)	Ocular Surface Disease Index	Symptom Assessment in Dry Eye	
		Mean± SD	Median (25%, 75%)	Severity Median (25%, 75%)	Frequency Median (25%, 75%)
<b>All (n)</b>	177	302.5 ± 14.3	4.6 (0.1, 10.3)	7.1 (1.1,19.1)	12.1 (4.0, 26.0)
<b>HT use (12 months)</b>					
Group 2A	90	302.7 ± 14.3	5.4 (1.2, 14.7)	11.0 (2.0,28.0)	17.5 (7.0, 29.0)
Group 2B	87	301.2 ± 13.7	4.3 (1.0, 7.6)	11.0 (1.0,12.0)	17.1 (1.0, 22.0)
Group 1	183	300.1 ± 12.6	4.2 (1.0, 7.3)	2.0 (0.0, 12.0)	6.3 (1.0, 23.0)
Difference 95% CI*		2.7 [-3.0, 8.3]	1.2 [-2.2, 5.3]	8.0 [2.3, 18]	12.5 [2.3, 19]
p-value*		0.39	0.27	0.02	0.001
<b>HT use (36 months)</b>					
Group 2A	90	303.9 ± 16.5	4.7 (1.0, 13.7)	12.7 (6.3,32.3)	23.0 (9.3, 32.0)
Group 2B	87	302.7 ± 12.5	4.6 (1.1, 12.2)	2.1 (0.1, 11.2)	6.1 (1.1, 14.0)
Group 1	183	299.7 ± 12.3	4.6 (0.0, 8.2)		
Difference 95% CI*		4.3 [-1.7, 9.7]	0.04 [-2.1, 4.2]	10.5 [6, 17]	15.1 [9, 21]
p-value*		0.16	0.54	0.0001	<0.001
<b>HT use (48 months)</b>					
Group 2A	90	305.4 ± 17.5	5.3 (2.1, 14.6)	14.0 (7.0,33.0)	22.5 (10.0,40.0)
Group 2B	87	302.7 ± 16.3	4.7 (0.0, 13.7)	12.1 (0.0,12.0)	20.3 (10.1,35.0)
Group 1	183	299.9 ± 11.7	3.3 (1.0, 10.6)	6.0 (1.0,11.0)	8.0 (1.1, 21.0)
Difference 95% CI*		5.7 [-0.02, 11.6]	1.2[-1.3,7.2]	12.1 [7, 29]	25.5 [6.5, 26.1]
p-value*		0.053	0.37	0.0003	0.003

There was a statistically significant difference between these two groups. Estrogen and progesterone HT users showed significant reduction in the number of patients with DES symptoms than estrogen-only users (p=0.001). Besides, there was a significant relationship in reduction of DES in HT users and non-users after 48 month treatment period (p=0.003).

\*95% confidence intervals (CI) calculated from the standard error of the difference for tear osmolality.

\*\*p-values calculated by t-test for tear osmolality and by Wilcoxon rank sums tests for others

**Table 3: ANOVA test results examining dosage levels of HT administration for postmenopausal women.**

	N	Mean	Standard	95% Confidence Interval of		P-Value
Difference in dosage levels of HT administration		M±SD	Error	Lower Bound	Upper Bound	
<1mg/day	71	69.03±25.48	3.02	63.0008	75.064	*< 0.001
>1mg/day	106	74.08±23.56	2.281	69.5432	78.6209	

\* Values are expressed at 95% confidence interval and are based on separate ANOVA and Welch and Brown-Forsythe tests for each outcome

Dosage levels <1 mg/day and > 1mg/day between HT E and HT Estrogen & Progesterone

**Table 4: ANOVA test results examining the variance in the duration of HT administration for postmenopausal women**

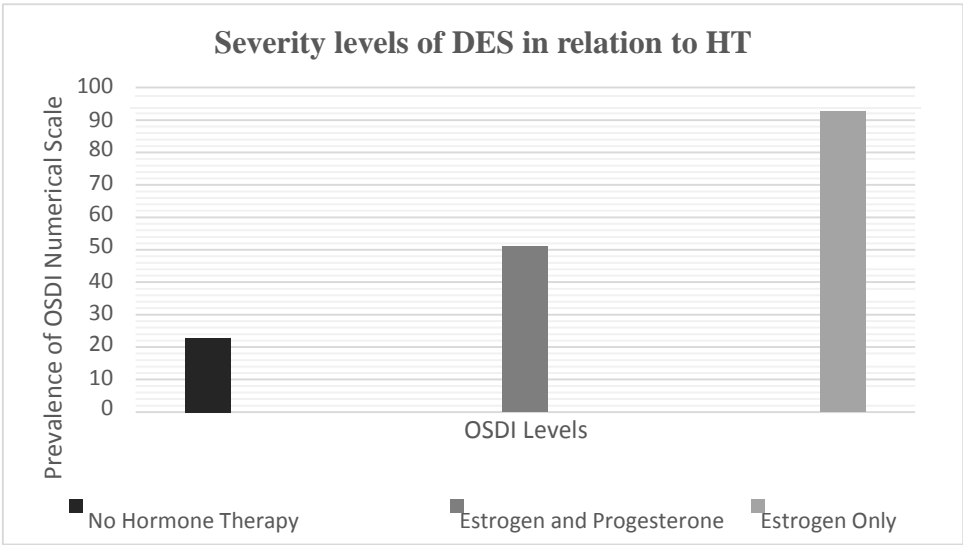
	N	M±SD	Standard Error	95% Confidence Interval of Mean		P-Value
Difference in duration of HT administration				Lower Bound	Upper Bound	
12 Months	47	61.23±25.93	3.78	53.61		< 0.001
36 Months	44	77.64±24.24	3.65	70.27		
48 Months	48	75.12±21.95	2.36	70.41		

The severity levels of DES among the study participants and their relationship to HT treatment is shown in Figure 1. Subjects that were administered with estrogen-only HT appear to have a higher OSDI compared to the subjects using a HT combination of estrogen and progesterone HT.

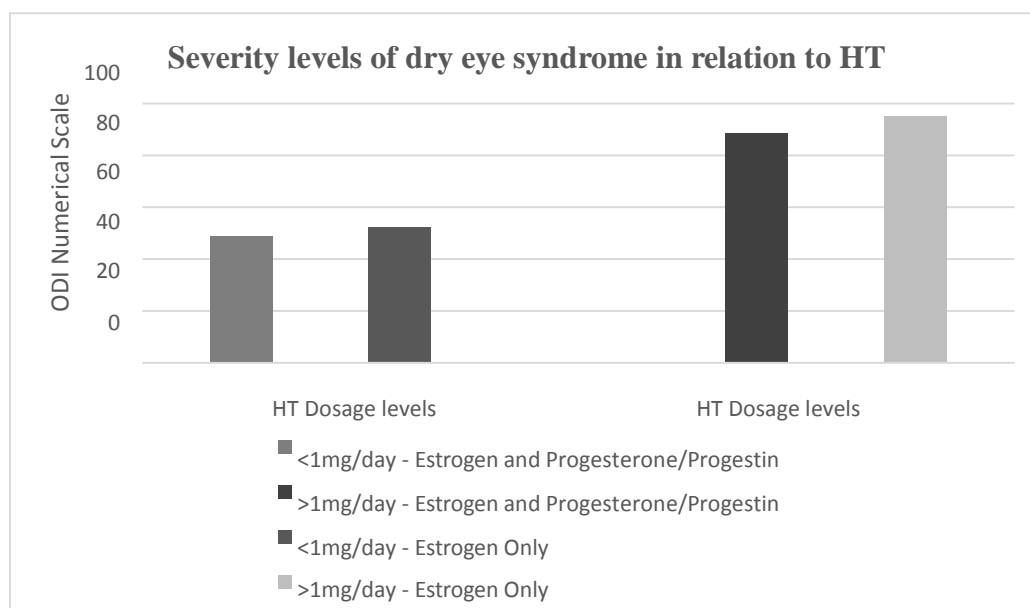
Dosage levels <1 mg/day and > 1mg/day between HT E and HT E & P; and duration 12,36 and 48 months between HT E and HT E & P.

\* Values are expressed at 95% confidence interval and are based on separate ANOVA and Welch and Brown-Forsythe tests for each.





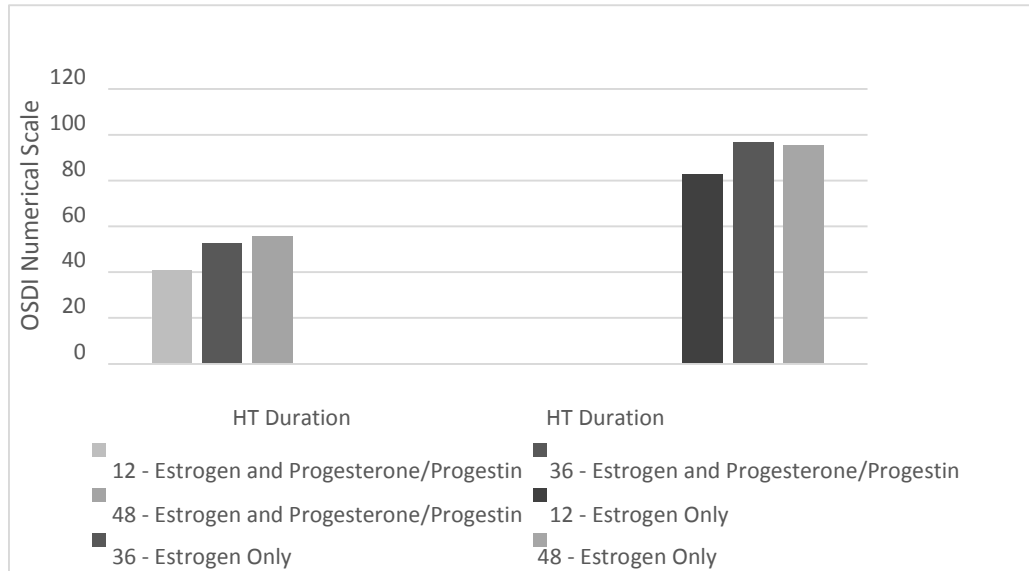
**Figure 1: Severity levels of DES in relation to HT usage in the control and study groups.**



**Figure 2: Severity levels of DES in relation to HT dosage levels among 360 Postmenopausal women**



### Severity levels of DES in relation to HT



**Figure 3: Severity levels of dry-eye syndrome in relation to HT use among 360 post-menopausal women**

